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10/580,711	05/18/2007	Klaus Benke	11987-00043-US	3892

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CONNOLLY BOVE LODGE & HUTZ, LLP
P O BOX 2207
WILMINGTON, DE 19899

EXAMINER	
BROWE, DAVID	

ART UNIT	PAPER NUMBER
1617	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/580,711	BENKE, KLAUS	
	Examiner	Art Unit	
	DAVID M. BROWE	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 November 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *November 1, 2010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This action is in response to Applicant's arguments in the reply filed November 1, 2010 to the Non-final Office Action mailed August 18, 2010. No claims have been amended, cancelled, or newly added. Claims 1-20 remain pending in the application.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Straub *et al.* (U.S. Patent Application Pub. No. 20030153610), in view of Yamamoto *et al.* (U.S. Patent No. 6,514,529) and Martin *et al.* (U.S. Patent No. 4,344,934).

Applicant Claims

Applicants claim a process for the preparation of a solid, oral pharmaceutical composition comprising 5-chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)-phenyl]-1,3-oxazolidin-5-yl}-methyl)-2-thiophenecarboxamide (e.g. "active compound I") in hydrophilized form comprising a) preparing granules comprising "active compound I" in hydrophilized form by moist granulation, and b) converting the granules into the pharmaceutical composition, if appropriate with addition of pharmaceutically acceptable additives. "Active compound I" is in crystalline and micronized form, is suspended in the granulating liquid, and introduced into a fluidized bed granulation. The resulting pharmaceutical composition is a rapid-release tablet.

Applicants also claim a solid, oral pharmaceutical composition comprising "active compound I" in hydrophilized, crystalline and micronized form; sodium lauryl sulphate as a wetting agent; and hydroxypropylmethylcellulose as a hydrophilic binding agent. The "active compound I", sodium lauryl sulphate, and hydroxypropylmethylcellulose are present in a concentration of 1-60%, 0.1-5%, and 1-15%, respectively, based on the total mass. The composition is a rapid-release tablet or a tablet covered with a coating.

Applicants further claim a method for the prophylaxis and/or treatment of thromboembolic diseases comprising administering an effective amount of the pharmaceutical composition or of "active compound I" in hydrophilized form.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

Straub *et al.* disclose a soild, oral pharmaceutical composition comprising 5-chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)-phenyl]-1,3-oxazolidin-5-yl}-methyl)-2-thiophenecarboxamide (e.g. "active compound I") (Pg. 2, sec. 0012-0018; Pg. 15, sec.

0363, 0367, 0369; Pg. 26, example 44), an oxazolidinone compound similar in structure to the antibiotic linezolid), and a method for the prophylaxis and/or treatment of thromboembolic diseases comprising administering an effective amount of the pharmaceutical composition of "active compound I" (Pg. 1, secs. 0009-0010; Pg. 14-15, sec. 0356; Pg. 15, sec. 0364; Pg. 16, sec. 0373).

Yamamoto *et al.* disclose a process for the preparation of a solid, oral pharmaceutical composition comprising an oxazolidinone compound, particularly the antibiotic linezolid, in hydrophilized form comprising *a)* preparing granules comprising a oxazolidinone compound in hydrophilized form by moist granulation, and *b)* converting the granules into the pharmaceutical composition, if appropriate with addition of pharmaceutically acceptable additives (abstract; Col. 1, lns. 29-36, 47-58; Col. 2, lns. 1-18, 64-65; Col. 3, lns. 5-7, 49-56, 65-67; Col. 4, lns. 1-4, 7-8; Col. 5, lns. 52-67; Col. 6, lns. 1-8, 19, 23, 41-53, 61-67; Col. 9, lns 10-30). The oxazolidinone compound is in crystalline form, is suspended in the granulating liquid, and introduced into a fluidized bed granulation (Col. 2, lns. 64-65; Col. 3, lns. 5-7; Col. 4, lns. 2-4; Col. 5, lns. 55-67). The resulting pharmaceutical composition is a rapid-release or coated tablet (Col. 1, lns. 29-31, 45-52; Col. 3, ln. 49; Col. 4, lns. 7-8; Col. 6, lns. 19, 23; Col. 9, lns. 10-30). Yamamoto *et al.* also disclose a solid, oral pharmaceutical composition comprising an oxazolidinone compound in hydrophilized and crystalline form, with hydroxypropylmethylcellulose as a hydrophilic binding agent. The oxazolidinone compound and hydroxypropylmethylcellulose are present in a concentration of 1-60% and 1-15%, respectively, based on the total mass (Col. 9, lns. 10-30). The composition

is a rapid-release tablet or a tablet covered with a coating (Col. 1, lns. 29-31, 45-52; Col. 3, ln. 49; Col. 4, lns. 7-8; Col. 6, lns. 19, 23; Col. 9, lns. 10-30).

Martin *et al.* disclose a process for the preparation of a solid, oral pharmaceutical composition comprising an active agent in hydrophilized form comprising *a)* preparing granules comprising the active agent in hydrophilized form by moist granulation, and *b)* converting the granules into the pharmaceutical composition, if appropriate with addition of pharmaceutically acceptable additives (abstract; Col. 3, lns. 14-22, 25, 27, 30-31, 40-50, 53, 55-62, 66-68; Col. 4, lns. 2-4, 7-15, 19-22, 31, 35-36; Col. 5, lns. 4-7, 29-30, 50-60, 63-67; Col. 6, lns. 9-12, 15-17, 21-24, 28-30, 44-47). The active agent is in crystalline and micronized form, is suspended in the granulating liquid, and introduced into a granulator (Col. 5, lns. 4-7, 29-30, 50-60, 63-67). Martin *et al.* also disclose a solid, oral pharmaceutical tablet comprising an active agent in hydrophilized, crystalline and micronized form; sodium lauryl sulphate as a wetting agent; and hydroxypropylmethylcellulose as a hydrophilic binding agent (Col. 16, lns. 42-45). The active agent, sodium lauryl sulphate, and hydroxypropylmethylcellulose are present in a concentration of 1-60%, 0.1-5%, and 1-15%, respectively, based on the total mass (Col. 6, lns. 21-24, 28-30, 44-47; Col. 15, lns. 54-57, 67-68).

Ascertainment of the Difference Between the Scope of the Prior Art and the Claims (MPEP §2141.012)

Straub *et al.* do not explicitly disclose the process of formulating “active compound I", and the composition thus formulated, in hydrophilized, crystalline and micronized form, together with sodium lauryl sulphate as a wetting agent, and

hydroxypropylmethylcellulose as a hydrophilic binding agent, which can be in the form of a rapid-release or coated tablet. These deficiencies are cured by the teachings of Yamamoto *et al.* and Martin *et al.*

Finding of Prima Facie Obviousness Rational and Motivation

(MPEP §2142-2143)

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of the present invention to combine the respective teachings of Straub *et al.*, Yamamoto *et al.*, and Martin *et al.*, outlined *supra*, to arrive at applicant's claimed invention.

Straub *et al.* disclose a soild, oral pharmaceutical composition comprising 5-chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)-phenyl]-1,3-oxazolidin-5-yl}-methyl)-2-thiophenecarboxamide (e.g. "active compound I"), an oxazolidinone compound strikingly similar in structure to the poorly water-soluble antibiotic linezolid; and pharmaceutically acceptable additives. Since Yamamoto *et al.* disclose that an oxazolidinone compound, particularly linezolid, in hydrophilized and crystalline form, can be advantageously formulated by moist granulation with hydroxypropylmethylcellulose into tablets that exhibit a significantly increased oxazolidinone bioavailability upon oral administration (abstract; Col. 1, lns. 46-50); and since Martin *et al.* disclose that poorly water-soluble antibiotics and other active agents; in hydrophilized, crystalline, and micronized form; can be advantageously formulated by moist granulation with hydroxypropylmethylcellulose and sodium lauryl sulphate into tablets that exhibit a significantly increased active agent bioavailability (abstract; Col. 3, lns. 14-17, 39-42;

Col. 6, lns. 15-17); one of ordinary skill in the art would be motivated to formulate 5-chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)-phenyl]-1,3-oxazolidin-5-yl}-methyl)-2-thiophenecarboxamide (e.g. "active compound I"); in hydrophilized, crystalline, and micronized form; by moist granulation with hydroxypropylmethylcellulose and sodium lauryl sulphate into tablets, with the reasonable expectation that the resulting tablets will successfully exhibit a significantly increased "active compound I" bioavailability upon oral administration.

In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a).

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Response to Arguments

Applicant's arguments filed November 1, 2010 have been fully considered but they are not persuasive.

i) Applicant asserts that "*rivaroxaban as in the present claims has much lower water solubility than linezolid*"; that "*linezolid is 'slightly soluble' and rivaroxaban, in contrast, is 'practically insoluble*'"; that "*a person of ordinary skill...would see this great discrepancy between solubility*"; and that "*The solubility differences rebut any*

suggestions that structural similarities would have motivated a skilled artisan to modify Straub et al to use the Yamamoto formulation".

The Examiner, however, would like to point out that rivaroxaban is an oxazolidinone agent; Yamamoto *et al.* are chiefly concerned with formulating oxazolidinone agents to optimize their bioavailability upon oral administration so that the blood levels of the oxazolidinone agent by oral administration are medically equivalent to the blood levels produced by IV administration (i.e. maximal). Yamamoto *et al.* provide examples of several specific oxazolidinone agents that share the oxazolidinone core structure and for which the formulation method is suitable for optimizing bioavailability as indicated. Thus, one of ordinary skill in the art would be motivated to formulate rivaroxaban, another oxazolidinone agent with the same oxazolidinone core structure, following the teachings of Yamamoto *et al.*, with the reasonable expectation that the resulting dosage form will also successfully exhibit an optimal bioavailability equivalent to that produced by IV administration. Because the Yamamoto *et al.* disclosure is not directed to only one specific agent with a very specific solubility, and because Yamamoto *et al.* never mention solubility at all, one of ordinary skill would not be particularly concerned with solubility, and would not make a significant distinction, when following the teachings of Yamamoto *et al.*, between oxazolidinone agents that are "slightly soluble" and those that are "practically insoluble".

ii) Applicant asserts that "*Martin is primarily concerned with formulation of griseofulvin*"; and that "*there would not be even a prima facie reason based on structure to use the Martin formulation with rivaroxaban*".

The Examiner, however, cannot agree that Martin *et al.* are primarily concerned with griseofulvin or its specific structure. Although Martin *et al.* employ griseofulvin as an illustrative example, it is clear to one of ordinary skill in the art that Martin *et al.* discloses a broad teaching of formulating agents that ordinarily provide poor bioavailability or are irregularly absorbed; and applies to a spectrum of agents of various solubilities, not just one agent in particular, such as griseofulvin, based on chemical structure. Thus, for example, Martin *et al.* disclose that their invention applies to "poorly water soluble and water-insoluble drugs". Because rivaroxiban is a poorly-water soluble drug, one of ordinary skill would be motivated to formulate rivaroxiban by employing the teachings of Martin *et al.*, with the reasonable expectation that the resulting dosage form will also successfully exhibit an enhanced bioavailability.

iii) Applicant asserts that "*Martin suggests that its process improves dissolution rate*"; that "*rivaroxaban tablets prepared by direct tabletting already had a good dissolution profile*"; and that "*Where dissolution rate is not a problem, then there is no suggestion to the ordinary skilled person that bioavailability can be increased by the method in Martin*".

The Examiner, however, would like to point out that Martin *et al.* are primarily concerned with improving the bioavailability of agents *in vivo* when orally administered. Martin *et al.* never explicitly state that the improvement in bioavailability is necessarily due to an enhanced dissolution rate of poorly-water soluble or water-insoluble drugs. Indeed, Martin *et al.* also disclose that their formulation is also good for more soluble drugs in need of enhanced bioavailability (see, for example, Col. 6, lns. 13-17).

For the reasons given above, the 35 USC 103(a) rejection of claims 1-20, of record, is hereby maintained.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Inquiries

Any inquiry concerning this communication or earlier communications from the examiner should be directed to DAVID M. BROWE whose telephone number is 571-270-1320. The examiner can normally be reached on Monday-Friday 7:30AM-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Fereydoun Sajjadi can be reached on 571-272-3311. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Carlos A. Azpuru/
Primary Examiner, Art Unit 1617

DAVID M. BROWE
Patent Examiner, Art Unit 1617